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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,750	03/20/2002	Nobuhiko Nakashima	3190-015	8810

33432 7590 07/08/2005

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,750	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9 and 12-31* is/are pending in the application.

4a) Of the above claim(s) *1-4,12-14,18,19,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,13,15-17,20-27,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Status of the Claims

2. Claims 1-4, 9 and 12-31 are pending.

Applicants' amendment filed on April 22, 2005 is acknowledged. Applicants' response has been fully considered. Claims 9, 13, 15-17, 20 and 25 have been amended, claims 5-8, 10 and 11 have been cancelled, and new claims 30 and 31 have been added. Claims 1-4, 12-14, 18, 19, 28 and 29 are non-elected inventions and withdrawn from consideration. Thus, claims 9, 13, 15-17, 20-27, 30 and 31 are examined.

Drawings

3. The formal drawings filed April 22, 2005 is acknowledged.

Foreign Priority Document

4. The foreign priority document, JAPAN 2001-016746, filed January 25, 2001 has been obtained and placed in the file.

Withdrawn Objection

5. The previous objection to the disclosure is withdrawn in view of applicant's amendment to the specification, and applicant's response at page 15 of the amendment filed April 22, 2005.

6. The previous objection to claims 5, 6, 10, 11, 13, 15 and 20-25 is withdrawn in view of applicant's amendment to the claims, applicant's cancellation of the claim, and applicant's response at pages 15-16 of the amendment filed April 22, 2005.

Withdrawn Claim Rejections - 35 USC § 112

7. The previous rejection of claims 5-8, 10 and 11 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's cancellation of the claims in the amendment filed April 22, 2005.

8. The previous rejection of claims 5-11, 16, 17, 20 and 22-24 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's cancellation of the claims, applicant's amendment of the claims, and applicant's response at pages 19-21 of in the amendment filed April 22, 2005.

Withdrawn Claim Rejections - 35 USC § 102

9. The previous rejection of claims 5-7 under 35 U.S.C. under 35 U.S.C. 102(b) as being anticipated by Sasaki *et al.* (J. Virology, 73, 1219-1226 (1999)), is withdrawn in view of applicant's cancellation of the claims in the amendment filed April 22, 2005.

Informality

The disclosure is objected to because of the following informalities:

10. Figs 1, 2 and 4 contain nucleotide sequences, however, the description of the drawings at page 5 of the specification does not identify these sequences with proper "SEQ ID NO:". Appropriate correction is required.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Previous rejection of claims 9, 13, 15-17, 20, 21, 24, 26 and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained, and claims 30 and 31 have been added. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Claims 9, 13, 15-17, 20, 21, 24, 26, 27, 30 and 31 are directed to a method of synthesizing a heterologous polypeptide *in vitro* utilizing a polynucleotide that promotes translation activity and has an RNA higher-order structure including PK (pseudoknot) I, II and III structures, wherein the RNA higher-order structure comprises a base sequence of SEQ ID NO:1-6 or 7, a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been modified and has a function for promoting a translation activity; or a method of initiating synthesis of arbitrary heterologous polypeptide comprising the step of changing a combination of base pairs that make up of PK I, II and III in a RNA higher order structure having the base sequence. While the specification indicates that the invention provides an RNA higher-order structure with promoting translation

activity and comprising a base sequence of SEQ ID NO:1-6 or 7, a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been modified and has a function for promoting a translation activity; and a method of synthesizing a heterologous polypeptide utilizing a polynucleotide having an RNA higher-order structure, wherein the synthesis is carried out in a cell-free protein synthesis system (pages 3-4), the specification does not disclose a genus of variants for an RNA higher-order structure with PK (pseudoknot) I, II and III structures and a function for promoting translation activity, or an RNA higher-order structure is made up of a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been mutated or altered in the claimed method.

The specification discloses the RNA higher-order structure having a function of promoting translation activity contains a base sequence of SEQ ID NO:1-7 (pages 6-7); the RNA higher-order structure containing three pseudoknot structures (PK I, II and III) contributes to the initiation and acceleration of translation of a protein (e.g., luciferase) *in vitro* and the mutation of PK I in the PSIV-IRES permits translation of a GFP gene, where in vitro translation was carried out using a rabbit reticulocyte lysate (Example 1; Figs. 7 and 8); and utilizing the mutated PSIV-IRES permitted translating a heterologous protein that begins with an arbitrary amino acid in cell-free system using a wheat germ extract (Example 2, Fig. 9), it does not describe a genus of variants for an RNA higher-order structure with PK (pseudoknot) I, II and III structures and a function for promoting translation activity, or an RNA higher-order structure is made up of a

base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been mutated or altered in the claimed method, nor discloses how to identify a functional polynucleotide among numerous polynucleotides related to the sequences of SEQ ID NO:1-7. A description of a specific higher-order RNA structure having a base sequence of SEQ ID NO:1 and a specific mutation in the in the PK I of PSIV-IRES does not provide original descriptive support for a genus of variants for a functional nucleotide sequence having an RNA higher-order structure in the claimed method. The disclosure of these base sequences of RNA higher-order structure and specific mutations in the PKI region of the base sequence does not meet the written description provision of 35 USC 112, first paragraph. The skilled artisan cannot envision all the contemplated nucleotide sequences for an RNA higher-order structure with PK I, II and III structures and a function for promoting translation activity based upon a specific RNA higher order structure of PSIV-IRES. Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Response to Argument

Applicants indicate the present specification contains a thorough explanation of what is meant by an RNA higher-order structure including PK (pseudoknot) I, II, and III structures, particularly in Example 1 at pages 14 - 15 and Figures 5 - 6. The genus of polynucleotides that contain the RNA higher-order structures including PK (pseudoknot) I, II, and III structures is thoroughly described on pages 4 - 8. Persons skilled in the art, and with knowledge of the basic principles of RNA base pair formation, can readily envision alterations that could be made in the structures described in Figures 5 and 6 and in sequences of SEQ ID NO: 1-7 or their complementary sequences that would retain the higher order structure. Further, the Examiner is clearly in error in asserting that the written description requirement requires a teaching of all of the possible nucleotide sequences for the RNA structures according to the present invention. The particular case laws cited by the Examiner are limited by their particular cases, that the claims in issue related to a DNA encoding a specific protein or specific class of proteins.

Applicants' response has been considered, however, the argument is not persuasive because the specification merely describes a specific higher-order RNA structure having a base sequence of SEQ ID NO:1 (Example 1, Figs. 15 and 16; pages 5-6) and a specific mutation in the in the PK I of PSIV-IRES (Fig. 7); and provides a general description regarding sequence homology and mutation on the base sequence (pages 7-8), it does not provide sufficient teachings on the identities of the functional polynucleotides related to the sequences of SEQ ID NO:1-7 and how to identify a functional polynucleotide among numerous polynucleotides related to the sequences of SEQ ID NO:1-7. The skilled artisan cannot envision all the

contemplated nucleotide sequences for an RNA higher-order structure based upon a specific RNA higher order structure of PSIV-IRES.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 13, 15, 21, 25, 26 and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 13, 15, 21, 30 and 31 are indefinite because of the use of the term "a base sequence hybridizing with the base sequences of 1) to 4) under stringent conditions". The cited term renders the claim indefinite, it is not clear under what condition the nucleotide sequence is hybridizing with the base sequence, and what nucleotide sequence the hybridized nucleotide has. Claim 13, 15 and 31 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Response to Argument

Applicants indicate the stringent hybridization conditions are defined on page 9 of the specification. Thus, persons skilled in the art upon reading the present specification would clearly know what conditions are required for hybridization. Moreover, the nature of the present invention is such that it is not crucial to know exactly what the nucleotide sequence is obtained by hybridization, since the polynucleotide that has a function of promoting translation is not a coding sequence. All that is necessary is that the polynucleotides have the higher order structure as clearly defined in the present specification.

Applicants response has been considered, however, the argument is not found persuasive because the specification (page 9) merely cites one example for the hybridization condition, it does not define this specific example as the only hybridization condition used, thus, it is not clear what condition is used for hybridization. Regarding the identity of the nucleotide sequence, which is obtained by hybridization and has a function of promoting translation, is not crucial, the argument is not persuasive because without the polynucleotide sequence, it is not clear how to identify a polynucleotide having a function of promoting translation.

14. Claim 25 is indefinite as to "positions 158-159 are gg instead of aa" for SEQ ID NO:1 because the sequence of SEQ ID NO:1 has aa at positions 159-160 instead of positions 158-159.

15. Claim 26 is indefinite because claim 26 has the same scope as the independent claim, claim 20.

Maintained Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Previous rejection of claims 9, 13, 15, 16, 20-23 and 26 under 35 U.S.C. 102(b) as being anticipated by Sasaki *et al.* (J. Virology, 73, 1219-1226 (1999)) is maintained. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Sasaki *et al* teach AUG-unrelated translation initiation is mediated by the internal ribosome entry site (IRES) of an insect picorna-like virus (i.e., *Plautia stali* intestine virus (PSIV)) *in vitro*, where the positive-strand RNA genome of the virus contains two non-

overlapping open reading frames (ORFs), and the capsid protein gene is located in the 3'-proximal ORF and lacks an AUG initiation codon (Fig. 1); the capsid protein gene was translated cap independently in the presence of the upstream cistron, indicating that the capsid protein is translated by internal ribosome entry; (pages 1220-1221; Figs 2 and 3). The reference also teaches a LUC (luciferase) gene was used as the second cistron, and in the CAT-IRES-LUC series of constructs, LUC genes without an AUG initiation codon was ligated to the PSIV sequences (Fig. 5; claims 9, 15, 16), and the LUC gene was efficiently translated when fused down stream of nt 6201 (pCAT-$IRES_{6201}$-LUC) and nt 6264 (pCAT-$IRES_{6264}$-LUC) in vitro (pages 1221-1222; Figs. 5 and 7; claims 20 and 26), where the $IRES_{6264}$ contains SEQ ID NO:1 (nt 6005-6204, 200 nucleotides; claims 13, 21, 22 and 23). Although the reference does not specifically indicate the $IRES_{6201}$ or $IRES_{6264}$ sequence of PSIV has an RNA higher-order structure (PK I, II or III), the $IRES_{6264}$ sequence contains SEQ ID NO:1 (or $IRES_{6201}$ sequence has at least 50 % homology to SEQ ID NO:1) and has the function of promoting translation activity, thus it would be expected that the IRES sequence has at least PK I, II or III structure, thus the reference anticipates the claimed invention.

Response to Argument

Applicants indicate Sasaki et al. confirms only the translation of a virus coat protein and luciferase genes as a fusion protein. As shown in the lanes 2 and 3 in Fig. 5, no protein synthesis via IRES was found in IRES6192-Luc and IRES6195-Luc. The abstract in the article states that the 3' terminus of IRES overlaps with the coat protein coding region only in a little part. The article brings an opposite result to the present invention. One important difference between the cited reference and the present invention is the finding that the structures of PKI, PKII, and PKIII

can be maintained to allow synthesis of a heterologous protein immediately from a codon following PKI even if a fusion gene part (nucleotide No. 6193-6201 in PSIV) of the virus coat protein gene is absent, resulting in bringing about an industrial applicability. Although the IRES higher order structure consisting of PKI, PKII, and PKIII is reserved in every virus, the reserved structure could not be found in the coat protein coding region of every virus. Fig. 5 in the cited reference does not anticipate the present invention, and actually teaches away by indicating that it is impossible to synthesize a protein starting with an arbitrary amino acid. Furthermore, the cited reference cannot anticipate the present invention because it lacks awareness of the existence of PKII and PKIII (pages 21-23 of the response).

Applicants' response has been considered, however, the argument is not persuasive because the reference teaches in CAT-IRES-LUC series of constructs, LUC genes without an AUG initiation codon was ligated to the PSIV sequences (Fig. 5), and the LUC gene was efficiently translated when fused down stream of nt 6201 (pCAT-$IRES_{6201}$-LUC, Fig. 5 lane 3) and nt 6264 (pCAT-$IRES_{6264}$-LUC, Fig. 5 lane 4) in vitro, where the $IRES_{6264}$ contains the same SEQ ID NO:1 as the claimed invention. Since the $IRES_{6264}$ of PSIV in the reference contains SEQ ID NO:1 having PKI, PKII and PKIII structures and has a function of promoting translation activity, thus it meets the criteria of the claimed method.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

17. Claims 9, 13, 15, 16, 20-24, 26, 30 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Sasaki *et al.* (PNAS 97, No. 4, 1512-1515 (February 2000)).

Sasaki *et al.* teach a group of positive-strained RNA viruses of insects lack an AUG translation initiation codon for their capsid protein gene, and the capsid protein of one of these viruses, *plautia stali* intestine virus (PSIV) is synthesized *in vitro* by internal ribosome entry site (IRES)-mediated translation (abstract, page 1513). In the construct pT7CAT-5375 (Fig. 1), the translation of the capsid protein in this virus is initiated with glutamine encoded by a CAA codon that is the first codon of the capsid-coding region, and the nucleotide sequence immediately upstream of the capsid-coding region (i.e., nucleotides 6188-6192) interacts with a loop segment (i.e., nucleotides 6163-6167) in the stem-loop structure located 15-43 nt upstream of the 5' end of the capsid-coding region to form pseudoknot structure which is essential for translation of the capsid protein (page 1513, claims 9, 13, 15, 16, 20-23 and 26). Various mutations in the pseudoknot structure have also been tested on IRES-mediated translation (Fig. 2), e.g., 6163_{CAU}-6190_{AUG} and 6163_{CUA}-6190_{UAG}, where efficient translation occurred (Fig. 2B, lanes 9 and 15; page 1513. right column; page 1514, left column; claims 24, 30 and 31). Although Sasaki *et al.* do not specifically recite the nucleotide sequence of SEQ ID NO:1, it is known that the IRES of PSIV contains SEQ ID NO:1, therefore, the reference anticipates the claimed invention.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
July 5, 2005